Scientific Abstract

This randomized, double-blind, placebo-controlled, dose-escalating clinical study will evaluate the effects of several dose levels of intramuscular pVGI.1(VEGF2) plasmid deoxyribonucleic acid (DNA) versus placebo with respect to safety and efficacy in patients with high-risk critical limb ischemia (CLI). The pVGI.1(VEGF2) plasmid contains the complementary DNA sequence for the vascular endothelial growth factor 2 (VEGF-2) protein, a member of a class of natural growth factors that promote angiogenesis. This study will obtain information regarding the safety, duration of activity, and optimal dose of pVGI.1(VEGF2) for the treatment of CLI.

The primary objectives of this study in adult patients with high-risk CLI (Rutherford Clinical Severity Score greater than or equal to 5) are as follows:

- To evaluate, through dose escalation in defined increments, the safety of intramuscular administration of pVGI.1(VEGF2) versus placebo by assessing the frequency, duration, and severity of adverse events

- To assess the effect of single, defined, increasing doses of pVGI.1(VEGF2) given by direct intramuscular injection into the affected leg when compared with placebo on leg ulcer healing (as assessed by ulcer surface area, time to complete healing, and ulcer score)

The secondary objectives of this study in adult patients with high-risk CLI are as follows:

- To assess the effect and/or duration of effect of single, defined, increasing doses of pVGI.1(VEGF2) given by direct intramuscular injection into the affected leg when compared with placebo on Rutherford Clinical Severity Score, ankle-brachial index (ABI), great-toe index (GTI), resting leg pain (as assessed by frequency of rest pain, pain medication use history, sleeping history, and intensity of rest pain), and the incidence and extent of lower leg amputation or other surgical interventions

- To evaluate the relationship between serum VEGF-2 protein levels and measures of safety and efficacy of pVGI.1(VEGF2)

Key inclusion criteria for patients in this study are CLI as defined by a Rutherford score of 5 or greater, nonhealing ulcers or other evidence of tissue loss in the ischemic leg, an ABI of less than 0.6 or a GTI of less than 0.3, and angiographic evidence of total occlusion in an artery of the affected leg. Key exclusion criteria are as follows: concomitant disease resulting in a life expectancy of less than 1 year; a history of neoplasm; evidence of retinopathy; a history of recent, successful aortic or lower extremity surgery or angioplasty; and presentation as a suitable candidate for surgical or angioplastic revascularization of the affected limb.

The study will consist of a Screening/Baseline Phase (up to 4 weeks), a Treatment Phase (1 day), and a Post-treatment Phase (12 weeks following treatment) and will include a maximum of 20 patients who will be enrolled sequentially into 3 dosing cohorts. The first 2 dosing cohorts (2 mg and 4 mg dose level) will consist of a minimum of 4 patients and a maximum of 8 patients. The last dosing cohort (8 mg dose level) will consist of 4 patients. Dosing in successive cohorts will occur after the first 4 patients in the preceding cohort have been evaluated for safety for at least 4 weeks following completion of the Treatment Phase. When dosing in the next cohort is begun, enrollment in the preceding cohort will be stopped.

Within each dosing cohort, patients will be randomized to receive either pVGI.1(VEGF2) or placebo in a 3:1 ratio. Three pVGI.1(VEGF2) dose levels will be used: 2, 4, or 8 mg. The patient will receive the total dose by 8 intramuscular injections into the affected limb given in a single treatment session.

An efficacy analysis will be conducted for all patients randomized into the study (*i.e.*, the intent-to-treat population). A secondary analysis for patients who complete the Weeks 4, 8, and 12 assessments of the Post-Treatment Phase will also be performed.